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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/754,711	01/12/2004	Deborah Kim Glencross	025455-113	1340

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EXAMINER	
FORD, ALLISON M	
ART UNIT	**PAPER NUMBER**
1651	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/754,711	GLENCROSS, DEBORAH KIM	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *3,4 and 6-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5 and 14-16* is/are rejected.

7)☒ Claim(s) *1,2 and 15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

Applicant's Request for Continued Examination filed 23 October 2006 has been received and entered into the case. The amendments to claims 1, 2 and 15 have been entered. Claims 1-16 remain pending, with claims 3, 4 and 6-13 being withdrawn from consideration. Claims 1, 2, 5 and 14-16 have been considered on the merits.

Priority

Acknowledgment is made of applicant's claim for priority as a continuation of PCT/IB/02/02725 filed on 11 July 2002, which further claims priority to South African national application 2001/5700, filed on 11 July 2001.

Response to Arguments

Applicants' arguments, received 23 October 2006, have been fully considered. Each argument will be addressed below, as appropriate; rejections or objections not repeated in this Action have been withdrawn and/or obviated by applicants' amendments. Applicants' discussions of improved between- and within-laboratory reproducibility of CD4+ lymphocyte counts using both single- and dual-platform approaches, reduced skill level (of technician) required to perform the method, and cost savings associated with use of an abbreviated panel, have also been noted and taken into consideration.

Regarding the rejection of claims 1, 2, 5 and 14-16 under 35 USC 112, second paragraph, for being indefinite, applicants amended the claims to obviate the cause of the rejections. However, the amendments have necessitated new grounds of rejection under 35 USC 112, second paragraph, as discussed below. The examiner has suggested alternative language to clarify what is believed to be the

intended method; the suggested version is only submitted to overcome *grammatical/technical* errors (i.e. the suggested language is not submitted to overcome the rejections based on the art).

Regarding the rejection of claims 1, 2, and 15-16 under 35 USC 102(b) over Melnicoff et al and the rejection of claims 2, 5, 14 and 16 under 35 USC 103(a) over Melnicoff et al, in view of Brando et al, applicants argue the Melnicoff et al reference inappropriately uses the term "leukocytes" in example 3A in place of the term "lymphocytes", and thus Melnicoff et al is not an enabling disclosure for the use of the total *leukocyte* population as a means for enumerating the number of CD4+ lymphocytes in a blood sample. In general, applicants argue that Melnicoff actually used the method outlined by Landay et al (Clin Immuno and Immunopath, 1989), which was recognized as the standard method for analyzing CD4+ lymphocytes via flow cytometry at the time; the method of Landay et al relies on total lymphocyte count (TLC), not total leukocyte count, as in the instant application. Though Melnicoff does not cite the method of Landay et al in Example 3A, they do cite the reference in Example 4, applicants rely on this citation, as well as reference in various other patents and applications owned by Zynaxis (assignee of Melnicoff '822), as evidence that the Landay et al method was the standard comparison method used in all of Zynaxis research and development, and thus was the comparative method described in Example 3A. Applicants present additional arguments supporting their position that Melnicoff ('822) erroneously and/or ambiguously used the term 'percent leukocytes' when they, in fact, meant 'lymphocytes'.

In response, while it is not conceded that Melnicoff erroneously or ambiguously used the term "percent leukocytes" or "total leukocyte count" when they actually meant "percent leukocytes that are lymphocytes" or "total lymphocyte count (TLC)", respectively, or that the Melnicoff et al reference cannot be relied upon for what it states, the rejections relying on Melnicoff et al are withdrawn for the following reason:

The claims have been amended to recite single- or dual-platform approaches to enumerate CD4+ lymphocytes from a cell population; each approach relying on a specific flow cytometric immunoanalysis method, which involves first establishing a primary gate to define all CD45+ cells, and then establishing a secondary gate, within the primary gate to define and identify CD4+ lymphocytes, by identifying those cells that have CD4(bright) expression, as well as low side scatter. As discussed in the examples, and exhibited in the figures, of the instant specification, CD4(bright)/low side scatter differentiates the CD4+ lymphocytes from the CD4+ monocytes, which often contaminate the results. Melnicoff et al do not teach or suggest using such a gating strategy, rather the method of Melnicoff et al Example 3A only separates out CD4+ cells, it does not have any additional steps or analysis methods to identify contaminating CD4+ monocytes.

Regarding the rejection of claims 1, 2, 5 and 14-16 under 35 USC 103(a) over Brando et al, in view of Barnett et al, applicants argue that neither Brando et al nor Barnett et al teach or suggest a method for CD4+ lymphocyte enumeration using the total leukocytes as the denominator; applicants further argue that neither reference indicate use of the total leukocyte population would improve the outcome or reproducibility of CD4+ lymphocyte measurements. Specifically applicants argue that Barnett et al refers to methods of identifying CD4+ lymphocytes by flow cytometric methods, wherein CD4+ lymphocytes are identified as CD3+CD4+, and does not use CD45 as a marker. Applicant also argues that Barnett et al teaches away from abbreviated panels (such as the instant invention), as it would result in loss of quality control checks. Furthermore, applicants argue that both Brando et al and Barnett et al teach away from use of dual platform systems for CD4+ lymphocyte analysis that involve use of a hematology analyzer, due to the inaccuracies coupled to use of hematology analyzers (e.g. human error). Finally, applicants point to a publication by Storie et al, which describes a PanLeucogating procedure which has higher internal quality control.

In response to applicants' arguments that neither Brando et al nor Barnett et al teach or suggest using total leukocyte counts as the reference population, it is again pointed out that Brando et al specifically stated that the reference population could be either leukocytes or lymphocytes, specifically exemplifying use of the pan-leukocyte marker CD45 for use in enumerating CD34+ cells (See Brando et al, e.g. Pg. 329, col. 2). It is noted that Barnett et al do not teach or suggest use of total leukocyte population as the reference population; however, the rejection of record was based on the teachings of Brando et al as the primary reference, Barnett et al was merely relied on as a secondary reference to support the statement that bead-based counting methods were considered to be superior to hematology analyzers for initial cell counting, due to the reduced probability of human error.

In response to applicants' arguments that Barnett et al teach away from use of abbreviated panels, it is again noted that Barnett et al was not relied upon to teach or suggest use of total leukocytes as the reference population, nor was Barnett et al relied upon to suggest the combination of CD45 (pan-leukocyte marker) and CD4 markers. However, it is noted that the argument that the instant invention relies on an abbreviated panel does not completely accurate- the instant invention uses the transitional language "comprising" therefore the claimed method, while it only specifies use of CD45 and CD4 markers, does not exclude use of other markers, such as CD3 or CD14; therefore, the currently claimed method is not limited to use of the recited markers, and thus is not necessarily an abbreviated panel.

In response to applicants' arguments that both Brando et al and Barnett et al teach away from use of dual platform methods, which rely upon use of hematology analyzers due to increased inaccuracies, it is first noted that a mere teaching or statement in the references that hematology analyzers (in dual platform methods) are prone to a higher error-rate, does not constitute teaching away, as they are not taught as unsuitable, or to render the method inoperable, there are merely recognized as less-desirable. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d

1130, 1132 (Fed. Cir. 1994). Second, it is further noted that the instant claims, particularly claims 1 and 15 are directed to, or include embodiments, utilizing a dual platform method (including use of a hematology analyzer). Therefore, though the references note problems associated with dual platform methods utilizing hematology analyzers, the reference is still applicable to the claimed embodiment, inferior or not.

In response to the citation of the Storie et al publication, it is not clear how such is applicable to rejection of record. Though Storie et al may have publicly acclaimed use of PanLeucogating at a post-filing date, this is not evidence that such was non-obvious at the time the invention was made.

However, though applicants' arguments were not found convincing for the reasons discussed above, the rejections of record over Brando et al, in view of Barnett et al, have been withdrawn for the following reasons:

The claims have been amended to recite single- or dual-platform approaches to enumerate CD4+ lymphocytes from a cell population; each approach relying on a specific flow cytometric immunoanalysis method, which involves first establishing a primary gate to define all CD45+ cells, and then establishing a secondary gate, within the primary gate to define and identify CD4+ lymphocytes, by identifying those cells that have CD4(bright) expression, as well as low side scatter. As discussed in the examples, and exhibited in the figures, of the instant specification, CD4(bright)/low side scatter differentiates the CD4+ lymphocytes from the CD4+ monocytes, which often contaminate the results. Neither Brando et al nor Barnett et al teach or suggest using such a gating strategy. The method of Brando et al relies on further separation of CD4+ monocytes through use of CD14 or CD13 markers; Brando et al did not identify the currently claimed gating strategy to identify CD4+ lymphocytes, but rather relied on excluding unwanted cells (See Brando et al, Pg. 329, col. 2). For this reason, the rejection of record is withdrawn.

Claim Objections

Claims 1, 2 and 15 are objected to because the claims use the terms "leucocyte(s)" and "haematology analyser" (British spellings). It is requested that the terms be changed to the American spellings: leukocyte(s) and hematology analyzer.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 5 and 14-16 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected because the language is unclear:

First, the claim uses both "CD45+ expressing cells" (line 4-5), "white blood cells" (lines 3, 8, and 22) and "CD45+ white blood cells" (lines 10-11 and 16) to refer to the same cell population; for purposes clarity and simplicity, applicants are requested to use a single term throughout.

Second, claim 1 uses the term "CD45+ expressing cells", this term is inappropriate. CD45+ (*positive*) denotes the cells express the CD45 marker; therefore, CD45+ **expressing** is duplicitous, and therefore can be considered indefinite.

Third, the term "bright CD4++/low side scatter expression" is inappropriate, as "bright" and "CD4++" are duplicitous, it is believed the appropriate term would be: "$CD4^{Bright}$/low side scatter expression". Otherwise, if applicants wish to use the term CD4++, such is considered indefinite in the context of the claim, as it is not clear if it is CD4+ lymphocytes or CD4++ cells are being identified.

Claims 2, 5, and 14-16 inherit the problems of claim 1, and therefore are rejected on the same grounds.

For claim 1, the following claim language is suggested:

"Claim 1. A method of enumerating the number of CD4+ lymphocytes in a cell sample, comprising:

(a) determining the absolute number of CD45+ cells in the cell sample by means of a hematology analyzer or via a flow cytometer;

(b) determining the proportion of CD45+ cells which are CD4+ lymphocytes via flow cytometry by:

(i) establishing a primary gate, defining all CD45+ cells;

(ii) establishing a secondary gate, within said primary gate, defining all CD4+ lymphocytes having $CD4^{Bright}$/low side scatter expression; and

(iii) calculating the proportion of CD45+ cells which are CD4+ lymphocytes;

(c) multiplying the absolute number of CD45+ cells, obtained in step (a), by the proportion of CD45+ cells which are CD4+ lymphocytes, obtained in step (b), thereby determining the absolute number of CD4+ lymphocytes in the cell sample."

Claim 2 is rejected because the language of the amendment is unclear:

A portion of amended claim 2 appears to present a method which contradicts that outlined in claim 1. Currently, step (b) of amended claim 1 requires the CD4+ lymphocyte count to be performed flow cytometrically; yet the portion of claim 2 that states "or whereby ... the proportion or percentage of CD4+ lymphocytes determined in step (b) is ... performed on a haematology analyzer." Clarification or removal of this embodiment in claim 2 is required.

For claim 2, the following claim language is suggested:

"Claim 2. The method according to claim 1, wherein step (a) determining the absolute number of CD45+ cells in the cell sample is performed via flow cytometry using a bead-based or volumetric-based counting method."

Dependent claim 14 should then read:

"Claim 14. The method according to claim 2, wherein the bead-based counting method comprises adding a known number of beads to the cell sample; and counting the beads and cells simultaneously to obtain the absolute CD45+ cell count."

Claim 16 is rejected because it is indefinite in light of the amendments to claim 1. Claim 1 no longer involves a step of determining the number of white blood cells per volume of blood in step (c).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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